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(54) Title: USE OF SPIPERONE AS AN IMMUNOSUPPRESSANT AND ANTI-INFLAMMATORY AGENT

(57) Abstract

A method for suppressing an immune response or of treating inflammation in a mammal by treating the mammal with an effective amount of spiperone; and a composition including CNS-blind spiperone.

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USE OF SPIPERONE AS AN IMMUNOSUPPRESSANT AND ANTI-INFLAMMATORY AGENT

Background of the Invention

The field of the invention is the suppression of immune and inflammatory responses.

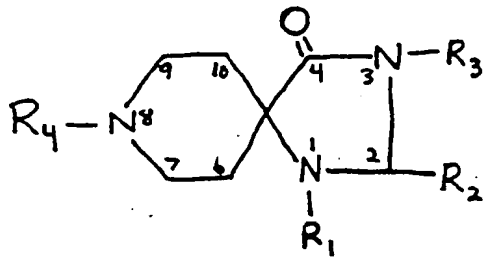
Although the immunological and inflammatory responses play vital roles in the protection of animals from infections and other externally-caused diseases, these responses can at times and under certain conditions cause undesirable pathological reactions with significant associated morbidity. Examples of such reactions include host rejection of foreign organ or tissue transplants; graft-vs-host disease in which donor immunological cells present in the graft attack host tissues; diseases with proven or possible autoimmune components, such as rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, psoriasis, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, multiple sclerosis, allergic encephalomyelitis, systemic lupus erythematosis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, scleroderma, Wegener granulamatosis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, Crohn's disease, Graves opthalmopathy, sarcoidosis, primary biliary cirrhosis, primary juvenile diabetes, uveitis posterior, and interstitial lung fibrosis; allergic asthma; inappropriate allergic responses to environmental stimuli such as poison ivy, pollen, insect

stings and certain foods; and inflammation resulting from any of the above immune reactions as well as from reaction to a physical agent such as occurs in sunburn or thermal, electrical, or chemical burns. Various therapeutics which have been utilized as immunosuppressants and anti-inflammatory agents include steroid hormones, anti-metabolites such as methotrexate and azathroprine, alkylating agents such as cyclophosamide and busulfan, and antibiotics.

Summary of the Invention

In general, the invention features a method for suppressing an immune response or of treating inflammation in a mammal (such as a human, or a domestic animal kept for companionship or commercial purposes: e.g., a dog or a cat) by treating the mammal systemically with an effective amount of spiperone. Such immunological or inflammatory responses may be attributable to, for example, diseases (herein termed "autoimmune diseases") with proven or possible autoimmune components, such as rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, psoriasis, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, multiple sclerosis, allergic encephalomyelitis, systemic lupus erythematosis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, scleroderma, Wegener granulamatosis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, Crohn's disease, Graves opthalmopathy, sarcoidosis, primary biliary cirrhosis, primary juvenile diabetes, uveitis posterior, or interstitial lung fibrosis, or may be

attributable to an allergy (e.g., allergic asthma), or to transplantation-related immunity (e.g., graft-versus-host disease or transplant rejection by the host). Other examples of inflammmation treatable by the method of the invention include cutaneous and mucosal inflammatory responses, which may be attributable to a condition involving an immune response, arthritis of any type, atopic dermatitis or other examples of dermatitis, allergic reactions, asthma of any type, or autoimmune diseases (in addition to those listed above), or which may be of unknown etiology. The spiperone used in the method of the invention preferably has the following formula:



wherein

R_1 = H, CH_3-, C_6H_5-, cyclohexyl, 4-$(OCH_3)C_6H_4$-, 3-$(CH_3)C_6H_4$-, 4-$(CH_3)C_6H_4$-, 4-X-C_6H_4-, $(CH_3)_2CH$-, $CH_3(CH_2)_3$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, or $(CH_3)_3C$-;

R_2 = H or CH_3;

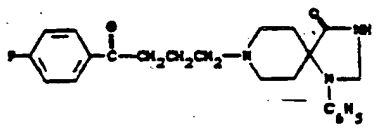
R_3 = H, CH_3, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, or $CN(CH_2)_2$-;

R_4 = H, $C_6H_5CH(CH_2CH_3)CH_2$-, $C_6H_5CH(CH_3)(CH_2)_2$-, $C_6H_5CH_2CH(CH_3)CH_2$-, $C_6H_5CH_2CH_2CH(CH_3)$-, $C_6H_5CH(CH_3)(CH_2)_3$-, 4-$CH_3C_6H_4CH(CH_3)(CH_2)_3$-,

$4\text{-}(CH_3O)C_6H_4CH(CH_3)(CH_2)_3$, $4\text{-}X\text{-}C_6H_4CH(CH_3)CH_2$-, $4\text{-}X\text{-}C_6H_4CH(CH_2CH_3)CH_2$-, $4\text{-}X\text{-}C_6H_4CH(CH_3)(CH_2)_2$-, $4\text{-}X\text{-}C_6H_4\text{-}CH(CH_3)(CH_2)_3$-, $C_6H_5CH(OCH_3)(CH_2)_2$-, $C_6H_5CH{-}CH\text{-}CH_2$-, $C_6H_5CO(CH_2)_3$-, $C_6H_5CO(CH_2)_4$-, $4\text{-}(CH_3)C_6H_4CO(CH_2)_3$-, $4\text{-}(CH_3O)C_6H_4CO(CH_2)_3$-, $4\text{-}X\text{-}C_6H_4CO(CH_2)_3$-, $4\text{-}X\text{-}C_6H_4CO(CH_2)_3$-, 2-thienyl-$CO(CH_2)_3$-, or $Ar_1\text{-}CH(CH_2)_n$-,

wherein n = 3 or 4; X = F, Cl, or Br; and each of Ar and Ar_1 is, independently, H, C_6H_5-, $4\text{-}(CH_3)C_6H_4$-, $4\text{-}(CH_3O)C_6H_4$-, $4\text{-}X\text{-}C_6H_4$-, $3\text{-}(CX_3)C_6H_4$-, 2-thienyl, or $4\text{-}X\text{-}C_6H_4CH_2$-.

and more preferably has the following formula:



(1)

The active compound may be a CNS-blind spiperone (defined below), and/or may be combined with a pharmaceutically-acceptable diluent or carrier.

When spiperone is derivatized or complexed in such a way as to make it largely incapable of inducing significant neuropharmacological side effects such as analgesia and neurolepsia, it is termed "CNS-blind spiperone". Such a composition preferably includes spiperone combined with a cycloamylase, such as cyclodextrin; the spiperone portion of the composition preferably has the general formula for spiperone set forth above, or more preferably the formula termed "spiperone (1)".

Spiperone is a known pharmaceutical which historically has been utilized clinically as a tranquilizer useful for the treatment of schizophrenia. As such, the safety and other salient characteristics of its use in humans are well documented. Besides its previously-known neuropharmacological activities, however, spiperone has been found to have significant ability to act systemically, in the method of the invention, as a suppressor of immune and/or inflammatory responses brought about by a variety of conditions, and thus has useful applications in the treatment of these conditions. The CNS-blind spiperone of the invention is capable of suppressing such immune and inflammatory responses without the concomitant undesireable neuropharmacological side effects, such as neurolepsia, induced by spiperone when it is not in a CNS-blind form.

Description of the Preferred Embodiments

The drawings are first described.

Fig. 1 is a bar graph illustrating the effect of systemic administration of spiperone on footpad swelling associated with IL-1-induced inflammation.

Fig. 2 is a bar graph illustrating the effect of systemic administration of spiperone on numbers of infiltrating inflammatory cells associated with IL-1-induced inflammation.

Fig. 3 is a bar graph illustrating the effect of systemic administration of spiperone on footpad swelling associated with PMA-induced inflammation.

Fig. 4 is a bar graph illustrating the effect of systemic administration of spiperone on numbers of infiltrating inflammatory cells associated with PMA-induced inflammation.

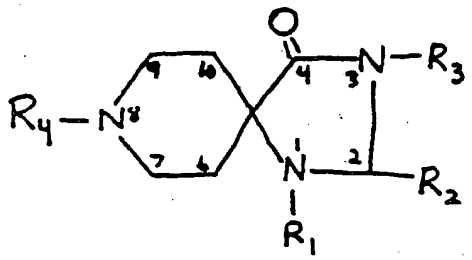
Fig. 5 is a bar graph illustrating the effect of systemic administration of spiperone on ear swelling associated with oxazolone-induced cutaneous contact hypersensitivity.

Fig. 6 is a bar graph illustrating the effect of systemic administration of spiperone on numbers of infiltrating inflammatory cells associated with oxazolone-induced cutaneous contact hypersensitivity.

Structure and Synthesis of Spiperone

The term "spiperone" herein denotes all of the molecules which are active in the method of the invention and which are the subject of the following U.S. patents: No. 3,155,669; No. 3,155,670; No. 3,161,644; and No. 3,238,216; all of which patents are hereby incorporated by reference. Methods for the synthesis of each such compound are disclosed in said four patents.

More particularly, forms of spiperone having the following formulae may be employed in the method of the invention:



wherein

R_1 = H, CH_3-, C_6H_5-, cyclohexyl, 4-$(OCH_3)C_6H_4$-, 3-$(CH_3)C_6H_4$-, 4-$(CH_3)C_6H_4$-, 4-X-C_6H_4-, $(CH_3)_2CH$-, $CH_3(CH_2)_3$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, or $(CH_3)_3C$-;

R_2 = H or CH_3;

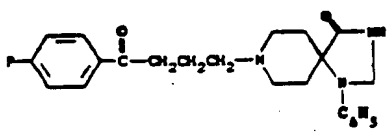
R_3 = H, CH_3, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, or $CN(CH_2)_2$-;

R_4 = H, $C_6H_5CH(CH_2CH_3)CH_2-$, $C_6H_5CH(CH_3)(CH_2)_2-$, $C_6H_5CH_2CH(CH_3)CH_2-$, $C_6H_5CH_2CH_2CH(CH_3)-$, $C_6H_5CH(CH_3)(CH_2)_3-$, $4-CH_3C_6H_4CH(CH_3)(CH_2)_3-$, $4-(CH_3O)C_6H_4CH(CH_3)(CH_2)_3$, $4-X-C_6H_4CH(CH_3)CH_2-$, $4-X-C_6H_4CH(CH_2CH_3)CH_2-$, $4-X-C_6H_4CH(CH_3)(CH_2)_2-$, $4-X-C_6H_4-CH(CH_3)(CH_2)_3-$, $C_6H_5CH(OCH_3)(CH_2)_2-$, $C_6H_5CH{-}{-}CH-CH_2-$ (with a CH_2 bridge), $C_6H_5CO(CH_2)_3-$, $C_6H_5CO(CH_2)_4-$, $4-(CH_3)C_6H_4CO(CH_2)_3-$, $4-(CH_3O)C_6H_4CO(CH_2)_3-$, $4-X-C_6H_4CO(CH_2)_3-$, $4-X-C_6H_4CO(CH_2)_3-$, 2-thienyl-$CO(CH_2)_3-$, or $Ar_1-CH(Ar)(CH_2)_n-$,

wherein n = 3 or 4; X = F, Cl, or Br; and each of Ar and Ar_1 is, independently, H, C_6H_5-, $4-(CH_3)C_6H_4-$, $4-(CH_3O)C_6H_4-$, $4-X-C_6H_4-$, $3-(CX_3)C_6H_4-$, 2-thienyl, or $4-X-C_6H_4CH_2-$.

Those forms of spiperone which are particularly useful in the method of the invention include those in which R_1 is C_6H_5-, $4-(X)-C_6H_4-$ or $4-(CH_3)C_6H_4-$; R_2 is H or CH_3; R_3 is H, CH_3, or CH_3CH_2-; and R_4 is $4-X-C_6H_4CO(CH_2)_3-$ or 2-thienyl-$CO(CH_2)_3-$; and especially those in which R_1 is C_6H_5-, $4-(Br)-C_6H_4-$, or $4-(Cl)-C_6H_4-$; R_2 is H or CH_3; R_3 is H, CH_3, or CH_3CH_2-; and R_4 is $4-X-C_6H_4CO(CH_2)_3-$ or 2-thienyl-$CO(CH_2)_3-$.

The particular form of spiperone used in Examples 1-3 is 8-[3-(p-fluorobenzoyl)propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one. Herein termed "spiperone (1)", this compound has the following structure:



(1)

The potential utility of any one of the above-described forms of spiperone as an immunosuppressant and/or anti-inflammatory agent can be conveniently determined by synthesizing the compound and testing it in one or more of the biological assays described in Examples 1-3.

Overcoming the Tendency of Spiperone to Affect the Central Nervous System

Spiperone has significant neuropharmacological properties, including analgesic and neuroleptic activities, which contributed to its historical use as a tranquilizer to treat schizophrenia, but which constitute generally undesirable side effects when it is employed as an immunosuppressive or anti-inflammatory agent. In an effort to increase the potency of these neuroleptic properties, Moerlein et al. (Int. J. Nucl. Med. Biol. 12:353-356, 1985) synthesized a number of forms of spiperone designed to increase the lipophilicity of the compound, and thus its potential ability to cross the blood-brain barrier. Their findings are also instructive for one selecting a compound to use in the method of the invention, for which the ability of the compound to cross the blood-brain barrier is ideally minimized. Other techniques for reducing the central nervous system (CNS) effects of spiperone include some established approaches known to the art, such as:

(a) increasing the size of the molecule via a covalent linkage to a large moiety (e.g., albumin or polyethylene glycol), using standard techniques of organic synthesis;

(b) increasing the overall hydrophilicity of the molecule by applying standard organic synthesis techniques to add one or more charged side chains onto the molecule or to alter an existing sidechain to make it more polar;

(c) a combination of (a) and (b); or

(d) forming a non-covalent complex with a cyclic molecule such as a cycloamylose (e.g., a cyclodextrin such as ß-cyclodextrin), which has a spacial arrangement of hydroxyl groups whereby the outer surface of the ring formed by the cycloamylose is hydrophilic and the inner surface is lipophilic. When utilized in aqueous solution, this structure permits molecules (or parts thereof), termed "guest molecules", which are less polar than water and which are of suitable dimensions, to be incorporated into the lipophilic inner cavity, such that the cycloamylose/ guest molecule complex presents to the blood-brain barrier as a relatively large and polar compound which is unable to penetrate the barrier. Such complexes may be prepared by any method known to the art, including those described in U.S. Patent No. 4,555,504, which discloses ß-cyclodextrin complexed with digoxin.

Spiperone altered or complexed by any of the above methods (with the effect of reducing the CNS effects of the compound to an acceptable level), and which exhibits the ability to supress an immune and/or inflammatory response, is referred herein to as "CNS-blind spiperone". The efficacy of any particular CNS-blind spiperone entity as an immunosuppressant or anti-inflammatory agent can be conveniently tested in any of the assays described in Examples 1-3 below. Whether or nor the same entity is capable of inducing the neuropharmacological side effects observed for

spiperone can be assayed by, for example, the hot plate test of Eddy et al., J. Pharmacol. 107:385(1953) and 110:135 (1954).

Therapeutic Composition

Spiperone can be provided in the form of pharmaceutically-acceptable salts or complexes. As used herein, the term "pharmaceutically-acceptable salts or complexes" refers to salts or complexes that retain the desired biological activity of the parent compound and exhibit minimal, if any, undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acids, naphthalenedisulfonic acids, and polygalacturonic acid; (b) base addition salts formed with polyvalent metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium, and the like, or with an organic cation formed from N,N-dibenzylethylene-diamine or ethylenediamine; or (c) combinations of (a) and (b); e.g., a zinc tannate salt or the like. The composition may be in the form of a pill, tablet, capsule, or liquid for oral administration; a cream, gel, lotion, spray, or ointment for application to the skin of a patient; a liquid capable of being administered nasally as drops or spray; or a liquid capable or intravenous, subcutaneous, parenteral, or intraperitoneal administration. The therapeutic composition can also be in the form of an

oil emulsion or dispersion in conjunction with a lipophilic salt such as a pamoic acid, or in the form of a biodegradable sustained-release formulation for subcutaneous or intramuscular administration. For maximum efficacy, zero-order release is desired. Zero-order release can be obtained using an implantable or external pump to administer the therapeutic composition.

Use

Spiperone and CNS-blind spiperone are capable of acting systemically to suppress the immune and inflammatory responses in animals. As such, they, or therapeutic compositions thereof, are useful for the treatment of a myriad of immunological and/or inflammatory disorders, including those related to host rejection of foreign organ or tissue transplants; graft-vs-host disease; autoimmune diseases, such as rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, psoriasis, autoimmune uveitis, multiple sclerosis, allergic encephalomyelitis, systemic lupus erythematosis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, scleroderma, Wegener granulamatosis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, Crohn's disease, Graves opthalmopathy, sarcoidosis, primary biliary cirrhosis, primary juvenile diabetes, uveitis posterior, and interstitial lung fibrosis; allergic reactions; and inflammation resulting from sunburn or thermal, electrical, or chemical burns.

Example 1: Inhibition of rIL-1-induced Inflammation

0.05 ml of phosphate-buffered saline ("PBS"; GIBCO, Grand Island, NY) containing 200 units of recombinant human interleukin-1 ("rIL-1"; Genzyme Corporation, Cambridge, MA; specific activity: 100,000 units/μg) was injected intradermally into the right hind footpad of each of 15 mice (C57BL/6J female mice, 6-8 weeks old: Jackson Laboratory, Bar Harbor, ME; or Balb/c female mice, 6-8 weeks old: Charles River Laboratories, Kingston Facility, Stoneridge, NY). An identical amount of PBS was injected into the left hind footpad of each mouse. At one hour after injection of the rIL-1, the right rear flank of each mouse was subcutaneously injected with one of the following: 0.1 ml of Cremophor EL (a pharmaceutical carrier, obtained from BASF Corp., NJ); 30 mg/kg of spiperone (1) (Sigma Chemical Co., St. Louis, MO) in 0.1 ml of Cremophor EL; or 150 mg/kg spiperone (1) in 0.1 ml Cremophor EL. At eight hours after rIL-1 injection, footpad thicknesses were measured with a spring-regulated engineer's micrometer. After measurement, mice were sacrificed and specimens of the right hind footpad tissue were fixed in 10% buffered formalin for at least 48 hours and then prepared for microscopic assessment of infiltrating cells using standard techniques of morphometry performed on paraffin-embedded and hematoxylin- and eosin-stained sections. Using an ocular grid, specimens were examined in a coded fashion, and all morphologically-identified inflammatory cells were quantified.

Systemic treatment with spiperone reduces the extent of rIL-1-induced inflammation, whether such inflammation is expressed as the difference ("Δ thickness") between measured thicknesses of the

right and left footpad of each mouse (Fig. 1), or by the degree of infiltration of inflammatory cells (Fig. 2). The Δ thickness after treatment with 30 mg/kg and 150 mg/kg spiperone was approximately 10% and 50% lower, respectively, than the Δ thickness seen with the untreated controls (Fig. 1), while the number of inflammatory cells per mm^2 of biopsied footpad tissue decreased by approximately 40% and 75% at the two respective dosage levels, compared to the untreated controls (Fig. 2).

Example 2: Inhibition of PMA-induced Inflammation

10µl of phorbol-12-myristate-13-acetate ("PMA", Sigma Chemical Co.), dissolved in acetone at 1 mg/kg acetone, was applied to the inner surface of the right ear of each of 15 Balb/c mice. At one hour after the PMA application, mice were treated systemically with spiperone (1) or carrier (Cremophor EL) as described in Example 1. Immediately before and at 18 hours after application of PMA, ear thicknesses were measured with a spring-loaded engineer's micrometer. "Δ Thickness" for ear swelling measurements represents the 18-hour value minus the baseline value. The mice were then sacrificed, and specimens of ear tissue were fixed in a fixative solution consisting of 2.0% paraformaldehyde, 2.5% glutaraldehyde, and 0.025% $CaCl_2$ in 0.1M sodium cacodylate buffer, pH 7.4, for 24 hours at 4°C. The specimens were stored in 0.1M sodium cacodylate buffer, pH 7.4, for an additional 24 hours, after which the old buffer was removed and fresh cacodylate buffer was added. Specimens were then prepared for microscopic quantification of morphologically-identified infiltrating inflammatory cells using standard techniques of morphometry performed on plastic-embedded and Giemsa-stained 1µm sections.

As shown in Fig. 3, spiperone at systemic doses of 30 mg/kg and 150 mg/kg is capable of reducing ear swelling related to PMA-induced inflammation by approximately 40% and 60%, respectively, compared to ear swelling observed in the controls which did not receive spiperone. In addition, inflammatory cell infiltration was decreased by about 20% and 65% in the ear tissues of mice treated with 30 mg/kg and 150 mg/kg spiperone, respectively (Fig. 4).

Example 3: Inhibition of Oxazolone-induced Contact Hypersensitivity

The abdomens of 15 Balb/c mice were shaved with electric clippers. 50µl of 4% w/w of oxazolone (Sigma Chemical Co.) in a 4:1 v:v acetone:olive oil solution was applied to the shaved abdomen and 5µl was applied to each hind footpad of each mouse. Five to seven days later, mice were challenged for contact hypersensitivity to oxazolone by applying 10µl of the 0.4% oxazolone solution to both the inner and the outer surfaces of the right ear of each mouse. At one hour after the oxazolone challenge, mice were treated systemically with spiperone (1) in carrier (Cremophor EL), or carrier alone, as described in Example 1. Immediately before and at 24 hours after the oxazolone challenge, ear thicknesses were determined with an engineer's micrometer to compute Δ thickness, as described in Example 2. Mice were sacrificed after measurements were obtained, and ear tissue was processed for determination of infiltrating inflammatory cells as described in Example 2.

As shown in Fig. 5, spiperone is capable of inhibiting ear swelling related to oxazolone-induced cutaneous contact hypersensitivity by approximately 68%

and 80% at systemic spiperone doses of 30 mg/kg and 150 mg/kg, respectively, compared to the degree of swelling exhibited by untreated control mice. The same dosages of spiperone inhibit inflammatory cell infiltration in oxazolone-challenged mice by approximately 35% and 80%, respectively, compared to the control mice which received no spiperone (Fig. 6).

Other embodiments are within the following claims.

What is claimed is:

1. A method for suppressing an immune response or of treating inflammation in a mammal, said method comprising treating said mammal systemically with an effective amount of spiperone.

2. The method of claim 1, wherein said immune response is attributable to an autoimmune disease.

3. The method of claim 2, wherein said autoimmune disease is selected from a group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, psoriasis, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, multiple sclerosis, allergic encephalomyelitis, systemic lupus erythematosis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, scleroderma, Wegener granulamatosis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, Crohn's disease, Graves opthalmopathy, sarcoidosis, primary biliary cirrhosis, primary juvenile diabetes, uveitis posterior, and interstitial lung fibrosis.

4. The method of claim 1, wherein said immune response is attributable to an allergy.

5. The method of claim 4, wherein said allergy is allergic asthma.

6. The method of claim 1, wherein said immune response is attributable to transplantation-related immunity.

7. The method of claim 6, wherein said transplantation immunity comprises graft-versus-host disease.

8. The method of claim 6, wherein said transplantation immunity comprises rejection of a transplant by said mammal.

9. The method of claim 1, wherein said inflammatory response is a cutaneous or mucosal inflammatory response.

10. The method of claim 1, wherein said inflammatory response is of unknown etiology.

11. The method of claim 1, wherein said inflammatory response is attributable to a condition involving an immune response.

12. The method of claim 1, wherein said inflammatory response is attributable to a condition selected from the group consisting of arthritis of any type; atopic dermatitis; allergic reactions; and autoimmune diseases.

13. The method of claim 12, wherein said condition is asthma of any type.

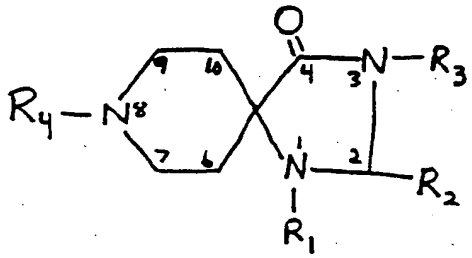
14. The method of claim 1 wherein said mammal is a human.

15. The method of claim 1 wherein said mammal is a domestic animal kept for companionship or commercial purposes.

16. The method of claim 15 wherein said mammal is a dog or cat.

17. The method of claim 1, wherein said spiperone is combined with a pharmaceutically-acceptable diluent or carrier.

18. The method of claim 1 wherein said spiperone has the following formula:



wherein

R_1 = H, CH_3-, C_6H_5-, cyclohexyl, 4-(OCH_3)C_6H_4-, 3-(CH_3)C_6H_4-, 4-(CH_3)C_6H_4-, 4-X-C_6H_4-, $(CH_3)_2CH$-, $CH_3(CH_2)_3$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, or $(CH_3)_3C$-;

R_2 = H or CH_3;

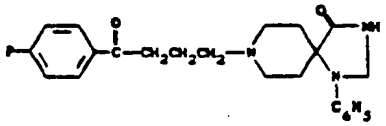
R_3 = H, CH_3, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, or $CN(CH_2)_2$-;

R_4 = H, $C_6H_5CH(CH_2CH_3)CH_2$-, $C_6H_5CH(CH_3)(CH_2)_2$-, $C_6H_5CH_2CH(CH_3)CH_2$-, $C_6H_5CH_2CH_2CH(CH_3)$-, $C_6H_5CH(CH_3)(CH_2)_3$-, 4-$CH_3C_6H_4CH(CH_3)(CH_2)_3$-, 4-($CH_3O$)$C_6H_4CH(CH_3)(CH_2)_3$, 4-X-$C_6H_4CH(CH_3)CH_2$-, 4-X-$C_6H_4CH(CH_2CH_3)CH_2$-, 4-X-$C_6H_4CH(CH_3)(CH_2)_2$-, 4-X-$C_6H_4$-$CH(CH_3)(CH_2)_3$-, $C_6H_5CH(OCH_3)(CH_2)_2$-, C_6H_5CH(-CH_2-)CH-CH_2-, $C_6H_5CO(CH_2)_3$-, $C_6H_5CO(CH_2)_4$-,

$4\text{-}(CH_3)C_6H_4CO(CH_2)_3\text{-}$, $4\text{-}(CH_3O)C_6H_4CO(CH_2)_3\text{-}$, $4\text{-}X\text{-}C_6H_4CO(CH_2)_3\text{-}$, $4\text{-}X\text{-}C_6H_4CO(CH_2)_3\text{-}$, 2-thienyl-$CO(CH_2)_3\text{-}$, or $Ar_1\text{-}CH(Ar)(CH_2)_n\text{-}$,

wherein n = 3 or 4; X = F, Cl, or Br; and each of Ar and Ar_1 is, independently, H, $C_6H_5\text{-}$, $4\text{-}(CH_3)C_6H_4\text{-}$, $4\text{-}(CH_3O)C_6H_4\text{-}$, $4\text{-}X\text{-}C_6H_4\text{-}$, $3\text{-}(CX_3)C_6H_4\text{-}$, 2-thienyl, or $4\text{-}X\text{-}C_6H_4CH_2\text{-}$.

19. The method of claim 18, wherein said spiperone has the following formula:



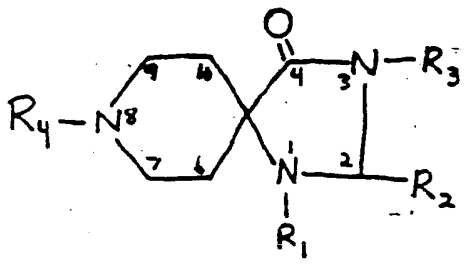
20. The method of claim 1, wherein said spiperone is CNS-blind spiperone.

21. A composition comprising a CNS-blind spiperone.

22. The composition of claim 21, wherein said CNS-blind spiperone comprises spiperone combined with a cycloamylase.

23. The composition of claim 22, wherein said cycloamylase is cyclodextrin.

24. The composition of claim 22, wherein said spiperone has the following formula:



wherein

R_1 = H, CH_3-, C_6H_5-, cyclohexyl, 4-$(OCH_3)C_6H_4$-, 3-$(CH_3)C_6H_4$-, 4-$(CH_3)C_6H_4$-, 4-X-C_6H_4-, $(CH_3)_2CH$-, $CH_3(CH_2)_3$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, or $(CH_3)_3C$-;

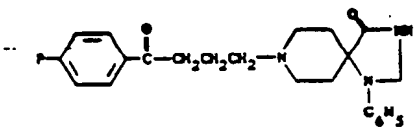
R_2 = H or CH_3;

R_3 = H, CH_3, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, or $CN(CH_2)_2$-;

R_4 = H, $C_6H_5CH(CH_2CH_3)CH_2$-, $C_6H_5CH(CH_3)(CH_2)_2$-, $C_6H_5CH_2CH(CH_3)CH_2$-, $C_6H_5CH_2CH_2CH(CH_3)$-, $C_6H_5CH(CH_3)(CH_2)_3$-, 4-$CH_3C_6H_4CH(CH_3)(CH_2)_3$-, 4-$(CH_3O)C_6H_4CH(CH_3)(CH_2)_3$, 4-X-$C_6H_4CH(CH_3)CH_2$-, 4-X-$C_6H_4CH(CH_2CH_3)CH_2$-, 4-X-$C_6H_4CH(CH_3)(CH_2)_2$-, 4-X-$C_6H_4$-$CH(CH_3)(CH_2)_3$-, $C_6H_5CH(OCH_3)(CH_2)_2$-, C_6H_5CH-CH-CH_2-, $C_6H_5CO(CH_2)_3$-, $C_6H_5CO(CH_2)_4$-, (with CH_2 bridging the two CH), 4-$(CH_3)C_6H_4CO(CH_2)_3$-, 4-$(CH_3O)C_6H_4CO(CH_2)_3$-, 4-X-$C_6H_4CO(CH_2)_3$-, 4-X-$C_6H_4CO(CH_2)_3$-, 2-thienyl-$CO(CH_2)_3$-, or Ar_1-$CH(CH_2)_n$-, (Ar)

wherein n = 3 or 4; X = F, Cl, or Br; and each of Ar and Ar_1 is, independently, H, C_6H_5-, 4-$(CH_3)C_6H_4$-, 4-$(CH_3O)C_6H_4$-, 4-X-C_6H_4-, 3-$(CX_3)C_6H_4$-, 2-thienyl, or 4-X-$C_6H_4CH_2$-.

25. The composition of claim 24, wherein said spiperone has the following formula:



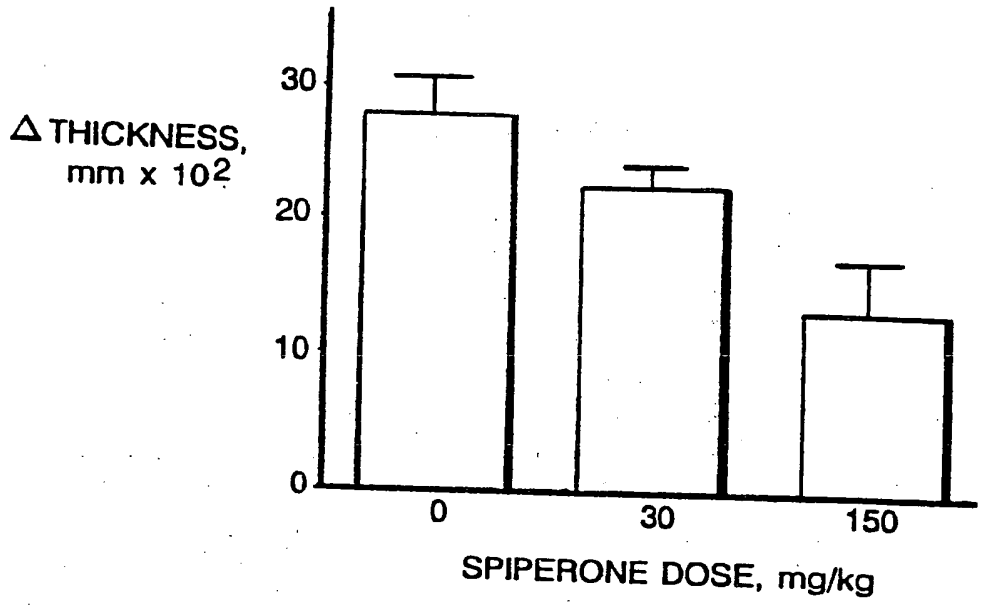


FIG. 1

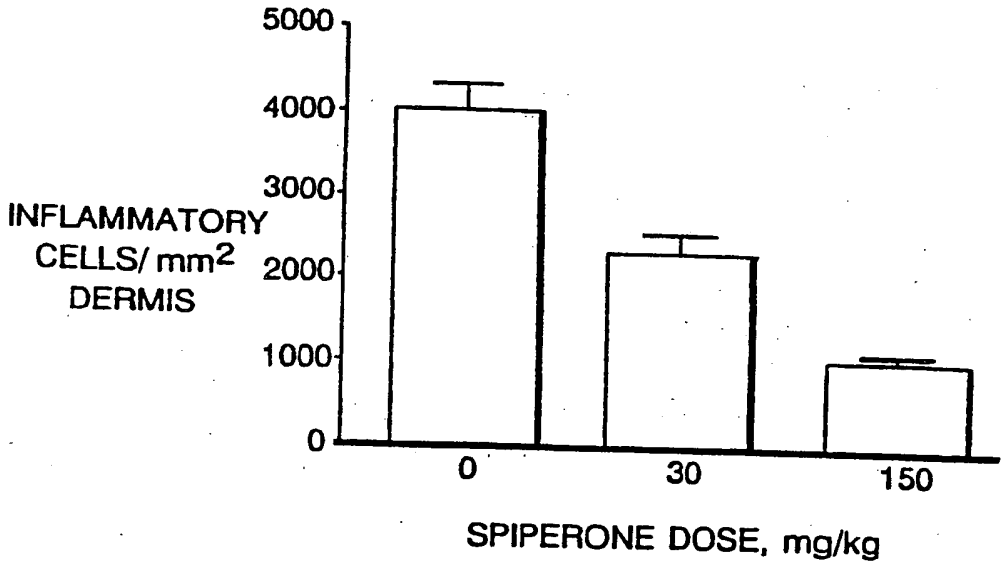


FIG. 2

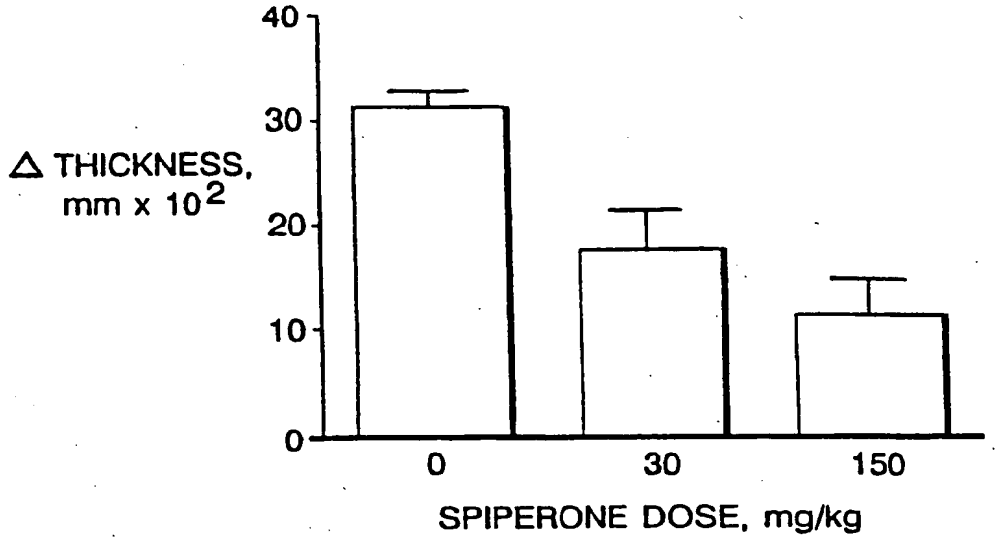


FIG. 3

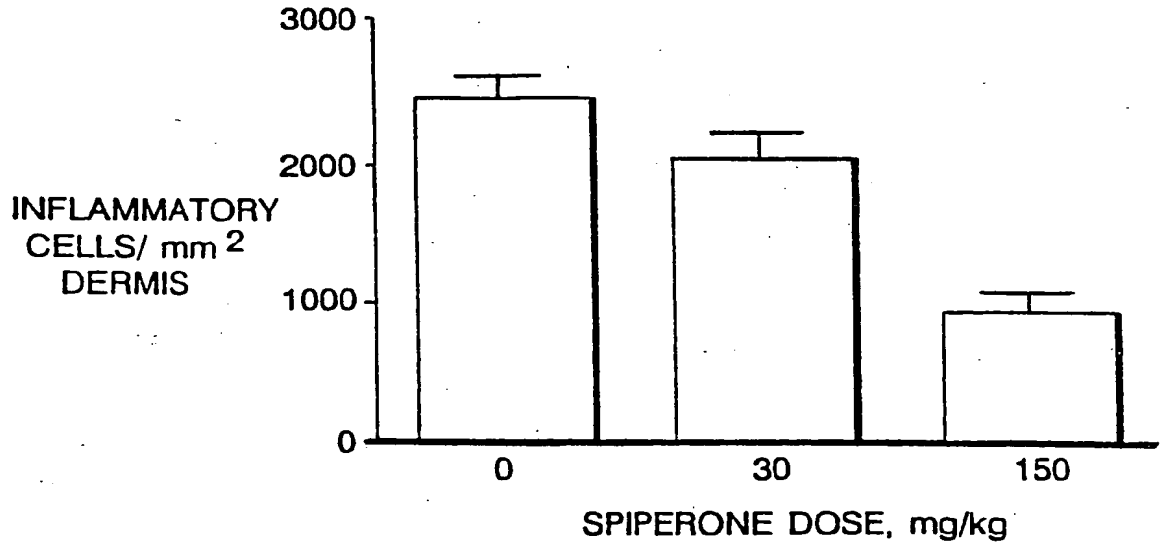


FIG. 4

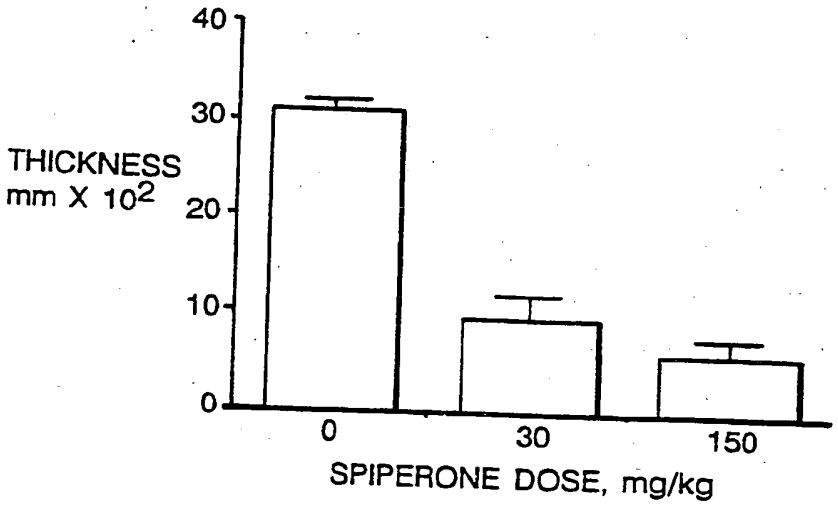


FIG. 5

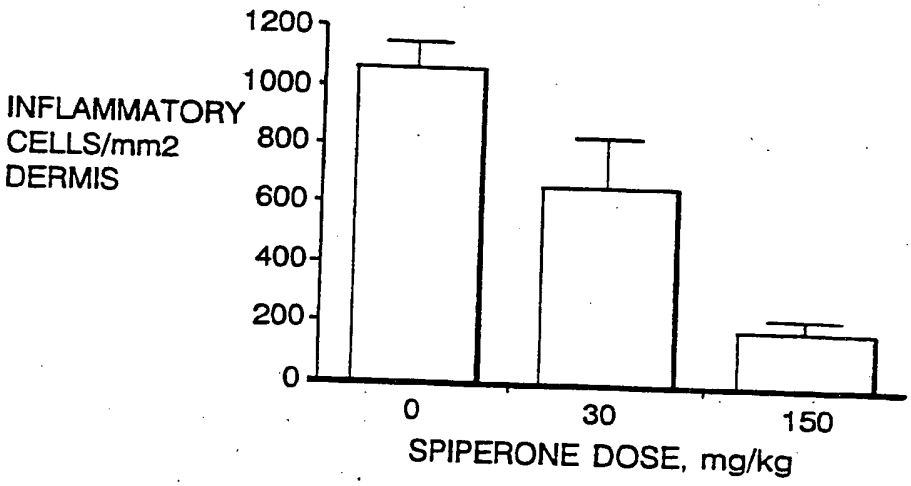


FIG. 6

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/01684

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. C. A61K 31/60 A61K 31/415
US CL: 514/59, 514/386

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
US	514/59, 514/386

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	US, A, 3,155,669 published 03 NOVEMBER 1964 (JANSSEN) See column 1&2.	21-25
Y	US, A, 3,155,670 published 03 NOVEMBER 1964 (JANSSEN) See column 1-4.	21-25
Y	US, A, 3,161,644 published 15 DECEMBER 1964 (JANSSEN) See column 1-3.	21-25
Y	US, A, 3,238,216 published 01 MARCH 1966 (JANSSEN) See column 1-4.	21-25
Y	US, A, 4,555,504 published 26 NOVEMBER 1985 (JONES) See entire document.	21-25

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 MARCH 1991	02 JUL 1991

International Searching Authority	Signature of Authorized Officer
ISA/US	For L. SCHENKMAN Ngotho Nguyen NGUYEN NGOC-HO INTERNATIONAL DIVISION

Form PCT/ISA/210 (second sheet) (May 1986)